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| APPLICATION NO.  | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO.   | CONFIRMATION NO. |
|--|-------------|----------------------|-----------------------|------------------|
| 09/804,700   | 03/13/2001  | Robert D. Ladner     | 266/176               | 1989             |
| 34055  | 7590        | 06/29/2004           | EXAMINER              |                  |
| PERKINS COIE LLP<br>POST OFFICE BOX 1208<br>SEATTLE, WA 98111-1208 |             |                      | CHUNDURU, SURYAPRABHA |                  |
|  |             |                      | ART UNIT              | PAPER NUMBER     |
|  |             |                      | 1637                  |                  |
| DATE MAILED: 06/29/2004  |             |                      |                       |                  |

Please find below and/or attached an Office communication concerning this application or proceeding.

SM-  
**Advisory Action**

**Application No.**

09/804,700

**Applicant(s)**

LADNER ET AL.

**Examiner**

Suryaprabha Chunduru

**Art Unit**

1637

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 04 June 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

**PERIOD FOR REPLY [check either a) or b)]**

- a) ☐ The period for reply expires \_\_\_\_\_ months from the mailing date of the final rejection.
- b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on \_\_\_\_\_. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☐ The proposed amendment(s) will not be entered because:
- (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);
  - (b) ☐ they raise the issue of new matter (see Note below);
  - (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
  - (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_.

3. ☐ Applicant's reply has overcome the following rejection(s): \_\_\_\_\_.
4. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☐ request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: none.

Claim(s) objected to: none.

Claim(s) rejected: 1-3, 5-8, 13-25.

Claim(s) withdrawn from consideration: \_\_\_\_\_.

8. ☐ The drawing correction filed on \_\_\_\_\_ is a) ☐ approved or b) ☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). \_\_\_\_\_.
10. ☐ Other: \_\_\_\_\_

JEFFREY FREDMAN  
PRIMARY EXAMINER

Continuation of 5. does NOT place the application in condition for allowance because: Applicants' arguments are not persuasive for the following reasons. Applicants' argue that the primary reference (Ladner et al. USPN. 5,962,246) impliedly teaches away from the instant invention drawn to the use of uracil-DNA glycosylase as a marker, as Ladner patent suggests a small likelihood of success. These arguments are fully considered and found not persuasive because as noted in MPEP 2123 states that A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill in the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). See also *Celeritas Technologies Ltd. v. Rockwell International Corp.*, 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir.1998) (The court held that the prior art anticipated the claims even though it taught away from the claimed invention. Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." *In re Gurley*, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). In the instant case Ladner et al. teach or suggest the limitations of the instant invention and the broader scope of the prior art does not constitute teaching away from the instant invention.

Further, Applicants argue that Ladner patent does not teach measurement of uracil incorporation in DNA and involvement of dUTPase in cell cycle check point arrest. Applicants' arguments are fully considered and found not persuasive. As discussed in the previous office action, Ladner teaches measuring cell proliferation or cell growth in cells treated and untreated with a compound that inhibits thymidylate metabolism in said cells, which indicates indirect measurement of the incorporation of uracil in DNA and cell cycle arrest. Further Ladner patent teaches non-proliferative cells have low dUTPase levels compared to proliferating cells (see column 9, lines 64-67, column 10, lines 1-6), indicating the role of dUTPase in cells. Applicants' arguments on different forms of dUTPase are irrelevant to the present context, because the instant claims are not directed to the measurement of each isoform of dUTPase, instead, the instant claims are drawn to a method for measuring dUTPase levels as a whole.

Applicants also argue that the secondary reference (Beck et al.) teach only the measurement of dUTPase and does not teach or suggest measuring dUTPase and uracil-DNA-glycosylase (UNG) simultaneously. Applicants' arguments are found not persuasive. Beck et al. reference was used in combination with Ladner et al. to show obviousness to use different cell lines expressing / or inhibiting uracil-DNA-glycosylase. In response to Applicants' arguments attacking the references individually, Examiner notes that one cannot show nonobviousness by attacking references individually where the rejections are based on combination of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed Cir.1986).

In the instant case the rejection is based on two references and the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir.1992). In this case, specific motivation is provided in the rejection, to combine a method of determining uracil misincorporation into DNA as taught by Ladner et al. with the various cells expressing/or inhibiting uracil-DNA glycosylase as taught by Beck et al. to achieve expected advantage of developing a sensitive method for characterizing uracil misincorporation into DNA because Beck et al. taught that association of thymineless state increases intracellular dUTP and dUMP levels with resulting uracil misincorporation into DNA and subsequent unrepaired excisions of uracils by uracil-DNA glycosylase lead to DNA fragmentation. An ordinary practitioner would have been motivated to combine the method of Ladner et al. with the method of Beck et al. to enhance the sensitivity of the assay by incorporating the additional parameters to support the uracil misincorporation into DNA because in addition to measuring dUTPase and dUTP levels, incorporation of the parameter UNG+ and UNG- cells would result in a better profile for characterization of a test compound and its role in misincorporation of uracil into DNA. Therefore the rejection is maintained herein for the reasons stated above.